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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C F.R § 1.53(b))

Attorney Docket No.	**PH-7103**
First Inventor or Application Identifier	Alan P. Carpenter Jr. et al.
Title	*GAS MICROSPHERE LIPOSOME COMPOSITES FOR ULTRASOUND IMAGING AND ULTRASOUND STIMULATED DRUG RELEASE*
Express Mail Label No	EL781891026US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ■ Fee Transmittal Form (e.g., PTO/SB/17) *(Submit an original and a duplicate for fee processing)*
2. ☐ Applicant claims small entity status. See 37 CFR 1.27.
3. ■ Specification [*Total Pages* 45] *(preferred arrangement set forth below)*
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to sequence listing, a table, or a computer program listing appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s) [*Total* 72]
   - Abstract of the Disclosure
4. ☒ Drawing(s) (35 U.S.C.113) [*Total Sheets* 3]
5. ☒ Oath or Declaration [*Total Pages* 1]
   a. ■ Unexecuted (copy)
   b. ☐ Copy from a prior application (37 CFR 1.63 (d)) *(for a continuation/divisional with Box 17 completed)*
      i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1 63(d)(2) and 1 33(b)
6. ☐ Application Data Sheet. See 37 CFR 1.76
7. ☐ CD-ROM or CD-R in duplicate, large table or Computer Program *(Appendix)*
8. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. ☐ Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ paper
   c. ☐ Statements verifying identity of above copies

ADDRESS TO

Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

ACCOMPANYING APPLICATIONS PARTS

9. ☐ Assignment Papers (cover sheet & document(s))
10. ☐ 37 C.F.R.§3.73(b)Statement *(when there is an assignee)* ■ Power of Attorney
11. ☐ English Translation Document *(if applicable)*
12. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
13. ☐ Preliminary Amendment
14. ■ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. ☐ Other:

17. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37 CFR 1.76:*

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No: _____ /

Prior application information: *Examiner* _____ *Group Art Unit:*

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

☒ *Customer Number 24348* or ☐ *Correspondence address below*

24348
PATENT TRADEMARK OFFICE

Name	Peter L. Dolan				
Address	DuPont Pharmaceuticals Company – c/o E.I. duPont de Nemours and Co.				
	1007 Market Street				
City	Wilmington	*State*	Delaware	*Zip Code*	19898
Country	U.S.A.	*Telephone*	(302) 992-4528	*Fax*	(302) 992-3999

Name (Print/Type)	Peter L. Dolan	*Registration No. (Attorney/Agent)*	46,307
Signature	Peter L. Dolan	*Date*	August 16, 2001

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08-1701

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FEE TRANSMITTAL for FY 2001

Patent fees are subject to annual revision

	Complete if Known
Application Number	Unknown
Filing Date	August 16, 2001
First Named Inventor	Carpenter et al.
Examiner Name	
Group / Art Unit	
Attorney Docket No	PH-7103

TOTAL AMOUNT OF PAYMENT ($) 1646 00

METHOD OF PAYMENT (check one)

1. ■ The Commissioner is hereby authorized to charge indicated fees and credit any over payments to

Deposit Account Number: 04-1928

Deposit Account Name: DuPont Pharmaceuticals Company

■ Charge Any Additional Fee Required Under 37 CFR 1 16 and 1 17

☐ Applicant claims small entity status See 37 CFR 1 27

2. ☐ Payment Enclosed.

☐ Check ☐ Credit card ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Fee ($)	Small Entity Fee Code	Fee ($)	Fee Description	Fee Paid
101	710	201	355	Utility filing fee	710 00
106	320	206	160	Design filing fee	
107	490	207	245	Plant filing fee	
108	710	208	355	Reissue filing fee	
114	150	214	75	Provisional filling fee	
				SUBTOTAL (1)	($) 710.00

2. EXTRA CLAIM FEES

			Extra Claims		Fee from below	=	Fee Paid
Total Claims	72	-**	52	X	18	=	936
Independent Claims		-3**	0	X		=	0
Multiple Dependent				X		=	936

Large Entity Fee Code	Fee ($)	Small Entity Fee Code	Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	80	202	40	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim, if not paid
109	80	209	40	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($).1646.00

**or number previously paid, if greater, For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Fee ($)	Small Entity Fee Code	Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for ex parte reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	390	216	195	Extension for reply within second month	
117	890	217	445	Extension for reply within third month	
118	1,390	218	695	Extension for reply within fourth month	
128	1,890	228	945	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive – unavoidable	
141	1,240	241	620	Petition to revive – unintentional	
142	1,240	242	620	Utility issue fee (or reissue)	
143	440	243	220	Design issue fee	
144	600	244	300	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	130	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	710	246	355	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	710	249	355	For each additional invention to be examined (37 CFR § 1.129(b))	
179 (RCE)	710	279	355	Request for Continued Examination	
169	900	169	900	Request for expedited examination of a design application	
				Other fee (specify)	

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($) 00

SUBMITTED BY				Complete (if applicable)	
Name (Print/Type)	Peter L. Dolan	Registration No. Attorney/Agent)	46,307	Telephone	302-992-4528
Signature	Peter Dolan			Date	August 16, 2001

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PH-7103

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Carpenter et al.

Case No.: PH-7103

Serial Number: Unknown

Group Art Unit: Unknown

Filed: August 16, 2001

Examiner: Unknown

For: GAS MICROSPHERE LIPOSOME COMPOSITES FOR ULTRASOUND IMAGING AND ULTRASOUND STIMULATED DRUG RELEASE

Wilmington, Delaware
Dated: August 21, 2001

PRELIMINARY AMENDMENT UNDER 37 CFR §1.111

Hon. Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a preliminary amendment to the above-mentioned U.S. non-provisional application filed August 16, 2001. Any payment related to this preliminary amendment should be charged or credited to Deposit Account No. 04-1928.

Amendments to the Specification:

At page 2, paragraph 3, line 16, please substitute this paragraph with the following paragraph:

Liquid and solid contrast agents containing entrapped gas are well known in the art. See, e.g., U.S. Patent No. 4,235,871; U.S. Patent No. 4,265,251; U.S. Patent No. 4,442,843; U.S. Patent No. 4,533,254; U.S. Patent No. 4,572,203; U.S. Patent No. 4,657,756; U.S. Patent No. 4,681,119; U.S. Patent No. 5,088,499; U.S. Patent No. 5,147,631; U.S. Patent No. 5,228,446; U.S. Patent No. 5,271,928; U.S. Patent No. 5,380,519; U.S. Patent No. 5,413,774; U.S. Patent No. 5,527,521; U.S. Patent No.

5,531,980; U.S. Patent No. 5,547,656; U.S. Patent No. 5,558,094; U.S. Patent No. 5,573,751; U.S. Patent No. 5,585,112; U.S. Patent No. 5,620,689; U.S. Patent No. 5,715,824; U.S. Patent No. 5,769,080; EP 0 122 624; EP 0 727 225; WO 96/40285; and WO 99/65467. The microbubbles provided by these contrast agents act as sound wave reflectors due to the acoustic differences between the gas microbubble and surrounding liquid.

Amendments to the Claims:

46. (Amended) A method of ultrasound imaging in a patient in need of such ultrasound imaging comprising:

administering to the patient an effective amount of a formulation of claim 1;

allowing a sufficient period of time for the circulation of the gas microsphere composite to reach the targeted area; and

performing ultrasound imaging on the patient.

51. (Amended) A method of treating heart disease, inflammation, infection, cancer or thromboembolic disease in a patient in need of such treatment comprising:

administering to the patient an effective amount of a formulation of claim 1, wherein one or more of the liquid-filled liposomes independently comprises a therapeutic agent;

allowing a sufficient period of time for the circulation of the gas microsphere composite to the targeted area; and

applying ultrasound energy to the region of pathology in the patient sufficient to cause the therapeutic agent to be released from the microsphere liposome composite at the region of pathology.

55. (Amended) A method for preparing a formulation of claim 1 comprising:

contacting a suspension of liposomes in a aqueous solution comprising at least one lipid or one surfactant; and

mixing the suspension with a gas that has a solubility of less than about 1.0% (v/v) in water at 25°C and 1 atm sufficient to provide the formulation.

59. (Amended) A method for preparing a formulation ofclaim 1 comprising:

contacting a suspension of liposomes in a aqueous solution comprising at least one therapeutic agent and at least one surfactant; and

mixing the aqueous liposome suspension with a gas that has a solubility of less than about 1.0% (v/v) in water at 25°C and 1 atm sufficient to provide the formulation.

63. (Amended) A kit for the preparation of a formulation of claim 1 comprising:

a container comprising an aqueous solution wherein the aqueous solution comprises at least one surfactant and liquid-filled liposomes; and

a means for introducing a gas that has a solubility of less than about 1.0% (v/v) in water at 25°C and 1 atm into the aqueous solution.

Remarks

This is a preliminary amendment to the above-mentioned U.S. non-provisional application filed August 16, 2001.

Claims 1-71 are pending.

The marked-up version of the specification is found in Appendix I, attached to this preliminary amendment, and titled "Marked-Up Version of Page 2, Paragraph 3, Line 16". The amendment is shown by text stricken through to indicate deletions and underlined text to indicate insertions.

The marked-up version of amended claims is found in Appendix II, attached to this preliminary amendment, and titled "Marked-Up Version of Rewritten Claims". The amendments are shown by text stricken through to indicate deletions and underlined text to indicate insertions.

The specification is amended at page 2, paragraph 3, line 16, to correct an obvious typographical error. Basis for the amendment is found throughout the specification, for example, on page 3, line 10. Accordingly, no new matter is added.

Claims 46, 51, 55, 59, and 63 are amended to cancel the multiple dependency of the claims. Support for the amendment is found throughout the application. Accordingly, no new matter is added. Applicants retain the right to pursue any cancelled subject matter during prosecution of the present application or in any continuation or divisional application.

Summary

Applicants submit that this application is in condition for allowance. A favorable action passing this case to issue is therefore respectfully requested. If a telephone interview would be of assistance in advancing prosecution of this application, Applicants' agent invites the Examiner to contact him at the number provided below.

Respectfully submitted,

Dated: August 21, 2001

Peter L. Dolan, Ph.D.
Agent for Applicants
REGISTRATION NO.46,307

Appendix I

Marked-Up Version of Page 2, Paragraph 3, Line 16

Liquid and solid contrast agents containing entrapped gas are well known in the art. See, e.g., U.S. Patent No. 4,235,871; U.S. Patent No. 4,265,251; U.S. Patent No. 4,442,843; U.S. Patent No. 4,533,254; U.S. Patent No. 4,572,203; U.S. Patent No. 4,657,756; U.S. Patent No. 4,681,~~199~~119; U.S. Patent No. 5,088,499; U.S. Patent No. 5,147,631; U.S. Patent No. 5,228,446; U.S. Patent No. 5,271,928; U.S. Patent No. 5,380,519; U.S. Patent No. 5,413,774; U.S. Patent No. 5,527,521; U.S. Patent No. 5,531,980; U.S. Patent No. 5,547,656; U.S. Patent No. 5,558,094; U.S. Patent No. 5,573,751; U.S. Patent No. 5,585,112; U.S. Patent No. 5,620,689; U.S. Patent No. 5,715,824; U.S. Patent No. 5,769,080; EP 0 122 624; EP 0 727 225; WO 96/40285; and WO 99/65467. The microbubbles provided by these contrast agents act as sound wave reflectors due to the acoustic differences between the gas microbubble and surrounding liquid.

Appendix II

Marked-Up Version of Rewritten Claims

46. (Amended) A method of ultrasound imaging in a patient in need of such ultrasound imaging comprising:

administering to the patient an effective amount of a formulation of ~~any one of~~ claim~~s~~ 1~~-45~~;

allowing a sufficient period of time for the circulation of the gas microsphere composite to reach the targeted area; and

performing ultrasound imaging on the patient.

51. (Amended) A method of treating heart disease, inflammation, infection, cancer or thromboembolic disease in a patient in need of such treatment comprising:

administering to the patient an effective amount of a formulation~~ of any one~~ of claim~~s~~ 1~~-45~~, wherein one or more of the liquid-filled liposomes independently comprises a therapeutic agent;

allowing a sufficient period of time for the circulation of the gas microsphere composite to the targeted area; and

applying ultrasound energy to the region of pathology in the patient sufficient to cause the therapeutic agent to be released from the microsphere liposome composite at the region of pathology.

55. (Amended) A method for preparing a formulation of ~~any one of~~ claim~~s~~ 1~~-45~~ comprising:

contacting a suspension of liposomes in a aqueous solution comprising at least one lipid or one surfactant; and

mixing the suspension with a gas that has a solubility of less than about 1.0% (v/v) in water at 25°C and 1 atm sufficient to provide the formulation.

59. (Amended) A method for preparing a formulation of ~~any one of~~ claim~~s~~ 1~~-45~~ comprising:

contacting a suspension of liposomes in a aqueous solution comprising at least one therapeutic agent and at least one surfactant; and

mixing the aqueous liposome suspension with a gas that has a solubility of less than about 1.0% (v/v) in water at 25°C and 1 atm sufficient to provide the formulation.

63. (Amended) A kit for the preparation of a formulation ~~of any one~~ of claim~~s~~ 1~~-45~~ comprising:

a container comprising an aqueous solution wherein the aqueous solution comprises at least one surfactant and liquid-filled liposomes; and

a means for introducing a gas that has a solubility of less than about 1.0% (v/v) in water at 25°C and 1 atm into the aqueous solution.